

have been found to be reduced.<sup>149</sup> The reason for this is not clear. Serum zinc levels are reduced in patients with hepatic dysfunction, and in such patients zinc excretion in urine is increased and hepatic zinc concentrations are reduced.<sup>150</sup> It has been suggested that a state of conditioned zinc deficiency exists in patients with liver dysfunction, and it is possible that oral contraceptive steroids, by altering hepatic zinc metabolism, produce a similar rate of zinc deficiency.

Another interesting aspect of the effect of contraceptive steroids on the liver is the tendency for these agents to increase mitochondrial delta-amino-levulinic acid synthetase (DALAS) activity.<sup>151</sup> Increased hepatic DALAS results in greater synthesis of heme protein and porphyrins<sup>151</sup> and increased urinary porphyrin excretion has been observed in women taking oral contraceptive steroid

drugs.<sup>151,152</sup> Oral contraceptives also can have an ameliorative effect on acute intermittent porphyria associated with the menstrual cycle or pregnancy.<sup>151</sup> Segal and Atkinson<sup>151</sup> have suggested that the increased heme synthesis may also enhance hepatic synthesis of microsomal cytochrome oxidase P-450, which is localized to smooth endoplasmic reticulum and involved in the metabolism of exogenous chemicals as well as endogenous substrates. But this has not yet been investigated.

Finally, there is a recent report of seven patients ranging in age from 25 to 39 years who presented with benign hepatomas after having taken oral contraceptive drugs for periods ranging from six months to five years.<sup>153</sup> Whether the oral contraceptive drugs played any role in the development of these tumors is unclear. Further study is necessary to clarify this problem.

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## Complications of Systemic Oral Contraceptive Therapy: Neoplasm—Breast, Uterus, Cervix and Vagina

MARK A. SPERLING, MD\*

ADMINISTRATION OF THE ACTIVE INGREDIENTS of oral contraceptive agents—namely, compounds with estrogen or progesterone-like actions, or ablation of their actions, has been used extensively in the treatment of cancer of the sex hormone target organs. This approach has not been entirely empirical, but is based on studies in animals which suggested that increases in the production of the sex hormones or alterations in their metabolism are important factors in the development of cancer of the sex hormone target organs. In the case of the oral contraceptive agents, these target organs include the breast, uterus, cervix and vagina, and much research has been done in an attempt to define the role of sex steroids in the production, prediction and remission of these cancers. Recently the evidence for and against the hypothesis impli-

cating abnormalities of secretion or metabolism of sex steroids in these cancers has been extensively reviewed and criticized.<sup>154</sup> This present overview is confined to a consideration of the potential carcinogenic effect of oral contraceptive agents in the induction of these cancers, and of the possibility that they may be important in reducing the risk factors for these malignant lesions.

### *Breast*

There is still considerable disagreement as to the endocrine status of women with carcinoma of the breast. The excretion of urinary estrogen metabolites by these patients has been reported to be high, normal or low.<sup>154,155</sup> It had also been postulated that the ratio of excreted estriol/estrone plus estradiol, might be important in the cause of the disease.<sup>156</sup> In a large demographic study, Asian women, who have a low incidence of mammary cancer, had a higher estriol ratio than American women, who have a much higher incidence of breast cancer.<sup>157</sup> However, more recently other investigators have disputed this conclusion.<sup>155</sup> In a study done by these investigators, total estrogen excretion in premenopausal women whose breast carcinoma was stage I to II was significantly lower than in normal controls. Post-menopausal women with breast carcinoma stage III-IV had a significant elevation of the estrone fraction. Conse-

\*Associate Chief, Pediatric Endocrinology, Harbor General Hospital; Assistant Professor of Pediatrics, UCLA School of Medicine.

quently, these investigators concluded that high estrogen excretion per se could not be an etiological factor in human breast carcinoma. In addition, they found a higher proportion of estriol in premenopausal patients with carcinoma of the breast in all stages, suggesting that estriol was not protective or antagonistic to other potential carcinogenic estrogens in humans. That estriol might be protective in preventing the appearance of breast carcinoma had been previously suggested.<sup>158,159</sup> Finally, in men with breast carcinoma, a significant increase of the estriol fraction with a corresponding reduction of the estrone fraction had been reported.<sup>160</sup> Thus, these studies argue against a clear contention that estrogens are a significant contributing factor in the pathogenesis of mammary cancer.

Similarly, studies of *in vitro* breast tissue metabolism are conflicting. Breast cancer tissue *in vitro* demonstrated increased estrogen uptake when compared with normal tissue in one study.<sup>161</sup> However, the uptake of <sup>3</sup>H estradiol by human breast tissue *in vitro* has been found to be very variable, with no correlation between uptake and histological classification of the tumor. Nor was uptake influenced by previous treatment with various androgens.<sup>154</sup> In humans, tumors have not been shown to have specific uptake of progesterone or testosterone, despite the occasional clinical response to testosterone therapy.<sup>154</sup> Nevertheless, *in vitro* studies have recently demonstrated that some breast cancer tissue is testosterone-dependent—that is, it is metabolically more active in the presence of testosterone added to the incubation medium—and that this tumor dependence can be inhibited by anti-androgens including estradiol.<sup>162</sup> When *in vitro* tumor dependence on testosterone was inhibited by estradiol, the clinical response to estrogen therapy was good; where the tumor survived well with estradiol *in vitro*, the clinical response to estrogen therapy was predictably poor. The mechanism for this protective effect of estrogens on some breast carcinomas is not known, but it may relate to estrogens ability to inhibit 5 alpha reductase,<sup>163,164</sup> the enzyme required for the final conversion of testosterone to its active metabolite dihydrotestosterone. The ability of normal or malignant breast tissue to synthesize testosterone and dihydrotestosterone has been recently demonstrated *in vitro*.<sup>165,166</sup>

With regard to the incidence or risk factor for the development of breast carcinoma among users of oral contraceptive agents, the recently pub-

lished report from the Boston Collaborative Drug Surveillance program showed that breast cancer had not developed in any of 4,700 young women taking oral contraceptive agents for more than five years.<sup>167</sup> Although these patients were relatively young, it does suggest that there is no evidence for a higher risk factor of breast carcinoma in women taking oral contraceptive agents than in non-users. Indeed, there was a negative association between the use of oral contraceptive agents and benign breast tumors, particularly for fibroadenoma. These findings are in accord with results of previously published studies where the incidence of fibrocystic and fibroadenomatous disease of the breast among oral contraceptive agent users was unaltered or diminished when compared with non-users.<sup>168-172</sup> In summary, despite many clinical investigations there is no direct link between oral contraceptive use and the development of breast carcinoma or fibroadenoma, nor are there untested alterations in the metabolism of estrogens by patients with mammary cancer or by the cancer itself, such that the estrogenic or progestogenic components of oral contraceptive agents could be implicated in the genesis or exacerbation of mammary cancer.

#### *Carcinoma of the Endometrium and Cervix*

There have been attempts to implicate alterations of estrogen secretion or metabolism as etiological factors in carcinoma of the endometrium and cervix. The amount of estrogen excreted in urine by women with cervical cancer has again been variously reported to be decreased, normal, or increased,<sup>173</sup> and minor alterations in estrogen metabolism have been reported and disputed.<sup>174,175</sup> It is fair to summarize that there are no biochemical data showing that high estrogen production is an etiological factor in these diseases. And the metabolism of estrogens is similar in patients with endometrial carcinoma and normal patients. However, there is one study purporting that carcinoma *in situ* of the uterine cervix was increased among users of oral contraceptive agents, but pre-therapy cytologic examinations were not done in this group of patients, and thus the study was not adequately controlled.<sup>176</sup> In contrast, there is evidence that synthetic progestogens depress mitosis in uterine cancer cells.<sup>177</sup> In general, there has been no correlation between human tumors and excretion of progesterone derivatives, although progesterone can act as a synergist or antagonist to certain animal tumors.

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TABLE 19.—Alterations in Serum Protein Concentrations in Women During Therapy with Estrogen-Progestogen Oral Contraceptive Preparations\*

Protein	Change in Concentration During Contraceptive Therapy
Thyroxine binding globulin .....	++
Prealbumin .....	±
Corticosteroid binding globulin .....	++
Testosterone-estradiol-binding globulin ..	++
Ceruloplasmin .....	+++
Transferin .....	+
Transcobalamin .....	+
Renin substrate .....	+++
Plasminogen .....	++
Fibrinogen .....	+
Alpha <sub>1</sub> antitrypsin .....	++
Beta <sub>2</sub> globulin .....	+
Hemopexin .....	+
Alpha <sub>2</sub> macroglobulin .....	+
Albumin .....	±
Alpha <sub>1</sub> acid glycoprotein .....	—
Orosomucoid .....	—
Haptoglobin .....	—

\*Modified from Lipsett et al: *Ann Intern Med* 74:251, 1971.

## Carcinoma of the Vagina

One very notable exception to the general exclusion of oral contraceptive agents as etiological factors in carcinoma of the vagina is the recent appreciation of the link between the use of certain synthetic estrogen-containing oral contraceptive agents in early pregnancy and the subsequent development of clear-cell vaginal carcinoma in the teen-aged daughters of the women who used them.

In 1970 Herbst et al reported on seven female patients aged 15 to 22 years with adenocarcinoma of the vagina, who had been seen at one hospital in the period 1966 through 1969.<sup>178</sup> This cancer, also referred to as clear-cell or endometrial type, is rare even in women over the age 50 years, in whom vaginal cancer is usually of the epidermoid type. The presenting symptoms and signs were prolonged vaginal bleeding, mistaken initially for anovulatory bleeding because it occurred in young women. Routine cytologic examination was negative, and the tumors were not palpable by rectal examination. Hence there was delay in correct diagnosis, which was made only at direct vaginal examination. Histologically the majority of tumors consisted of tubules and glands lined by clear cells containing glycogen. There was also a high prevalence of vaginal adenosis in these patients.

In a carefully controlled epidemiological investigation, Herbst et al discovered that seven of eight mothers whose daughters had vaginal adenocarci-

noma had taken estrogens in the early part of the pregnancy, while none of four matched controls for each patient had taken estrogens. Diethylstilbestrol, the synthetic estrogen, was shown to be the offending agent in the majority of cases.<sup>179</sup>

Statistical analysis indicated that the association of taking diethylstilbestrol during pregnancy and subsequent development of adenocarcinoma of the vagina in the daughters was highly significant ( $p < 0.00001$ ). Maternal bleeding during pregnancy and a history of involuntary abortion in a previous pregnancy were also significant factors. Smoking, exposure to x-rays, age, and breast feeding were not significant factors. Of eight women whose daughters had vaginal adenocarcinoma, there was only one who had neither taken stilbestrol during pregnancy nor had previous pregnancy loss. More, the tumors were known to occur rarely before the availability of estrogen therapy.<sup>179</sup> The stilbestrol used was taken during the years 1946-1951. During this interval 675 out of a total of 14,500 patients at a large women's hospital (a ratio of 1:21) had stilbestrol prescribed. From this, the risk factor would appear not to be very high although more and more cases are now being discovered.

The high prevalence of benign vaginal adenosis with these adenocarcinomas suggested that an anomaly of vaginal epithelium development might be a predisposing factor. An association between adenosis and clear-cell carcinoma of the vagina had previously been described in older women.<sup>180</sup> It was also suggested that the association of adenosis with the estrogenic effect of stilbestrol supported a Mullerian rather than mesonephric origin for these tumors. It was conjectured that the mechanism for the estrogenic induction of subsequent tumor in these patients might be either (1) that an increase in adenosis at menarche caused a predisposition to malignant change, or (2) that stilbestrol altered fetal vaginal cells, these changes manifesting as malignant disease years later. Finally, it was predicted that since estrogens were used widely in high-risk pregnancy during those years, it might be that increasing numbers of women with these tumors would be recognized as the at-risk population increased. In a further follow-up reported in 1972<sup>181</sup> these same investigators gave a fuller account of this tumor based on data from a registry that was established for the purpose of documenting the condition. Pregnancy histories were obtained on 66 of 91 cases in patients aged 8 to 25 years (mean age 17 years), and it was

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learned that 49 of the mothers had received diethylstilbestrol or related drugs, nine had received other unidentified medications for bleeding or prevention of pregnancy loss, and only eight had had no recorded medication during pregnancy. A high incidence of vaginal adenosis in these patients was confirmed, which strengthened the suggestion that abnormal development of Mullerian epithelium was the focal point of origin for these tumors. Even though follow-up periods were brief, the data showed that 17 of 65 patients had died or had recurrence of the disease. The results of the investigations are summarized in Tables 20 through 22. Vaginal bleeding was again the most common presenting symptom (Table 21). However, 13 of 91 patients were asymptomatic and diagnosis was made by direct pelvic examination. In addition, vaginal cytologic examination was negative in nine out of 30 cases. The dose of drugs varied widely but it can be seen that none were of the steroidal varieties (Table 20); they were all synthetic estrogen-like compounds. The duration of drug therapy varied from 12 days to through-

out term, and in all cases hormone therapy was started before the fourth month of pregnancy. The survival data are summarized in Table 22. Of 65 patients for whom data are available, 79 percent of those with vaginal carcinoma had survived, and 64 percent with cervical carcinomas had survived without recurrence. The follow-up period has been less than two years in many cases. It is to be noted that 26 percent of all patients had recurrence or died despite therapy (Table 22). The factors of size of tumor, depth of invasion and architectural pattern bore no statistically inordinate relationship to either node metastasis or survival. Mitotic activity, invasion of lymphatic channels and regional lymph node metastasis were important prognostic factors. The superficial location predominantly on the anterior vaginal wall was further evidence that the tumor was of Mullerian rather than mesonephric origin, since the mesonephric tumors occupy lateral or antero-lateral locations and are usually deeply situated.

As a result of these findings, screening programs have been set up in various centers in this country

TABLE 20.—Data on Medication During Pregnancy of Mothers Whose Daughters Had Vaginal or Cervical Carcinoma in Their Youth\*

Pregnancy Therapy	Total Cases	Location of Carcinoma	
		Vagina	Cervix
Stilbestrol .....	45	30	15
Dienestrol .....	2	1	1
Stilbestrol and dienestrol .....	1	1	..
Hexestrol .....	1	1	..
Medication for bleeding or previous miscarriage (type unknown) ..	9	4	5
None .....	8	4	4
<b>TOTALS</b> .....	<b>66</b>	<b>41</b>	<b>25</b>
History not obtainable .....	3	2	1
<b>TOTALS</b> .....	<b>69</b>	<b>43</b>	<b>26</b>
Investigation not complete .....	22		
<b>TOTALS</b> .....	<b>91</b>		

\*Reprinted by permission from Herbst AL, et al: N Engl J Med 287:1259, 1972.

TABLE 21.—Pre-therapy Symptoms and Result of Cytologic Examination\*

Symptoms	Number of Cases	Grade of Cytologic Smear	Number of Cases
Bleeding or discharge .....	54	IV or V (positive) .....	11
Mass .....	1	IIR or III (doubtful) .....	10
None .....	13	I or II (negative) .....	9
Unknown .....	23	Not done .....	15
<b>TOTALS</b> .....	<b>91</b>	Unknown .....	46
			<b>91</b>

\*Reprinted from Herbst AL, et al: N Engl J Med 287:1259, 1972

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TABLE 22.—*Staging and Survival after Therapy\**

Location of Cancer	Number of Cases	Patients Living and Free of Disease		Patients with Recurrences†	Dead Patients
		<2 yr	≥2 yr		
Vagina:					
Stage I . . . . .	28	14	12	2	0
Stage II . . . . .	12	2	6	1	3
Stages III & IV . .	3	0	0	0	3
TOTALS . . . . .	43	16	18	3	6
Cervix:					
Stage I . . . . .	6	4	2	0	0
Stage II . . . . .	11	6	0	1	4
Stages III & IV . .	5	0	2	1	2
TOTALS . . . . .	22	10	4	2	6

\*Reprinted from Herbst AL, et al: *N Engl J Med* 287:1259, 1972.

†Treated for or living with recurrence.

and internationally. The association between diethylstilbestrol ingestion in early pregnancy and the subsequent development of vaginal carcinoma in girls and young women has now been confirmed from a variety of centers in this and other countries.<sup>182,183</sup> It is clear that abnormal bleeding in adolescent girls must now be fully investigated, and that certain oral contraceptive agents play a role in the genesis of vaginal malignant disease.

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